Nuclear Medicine in Cancer Diagnosis and Therapy

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Abstract. Early cancer diagnosis remains one of the most actual problems of medicine, since it allows using the most effective methods of cancer treating. Unlike most diagnostic methods used in oncology, the methods of nuclear medicine allow assessing not so much the anatomic changes in the organ as the disturbance of metabolic processes in tumors and surrounding tissues. The authors describe the main radiopharmaceuticals used for diagnose and radiotherapy of malignant tumors.

Early cancer diagnosis remains one of the most urgent problems of medicine, since it allows using the most effective methods of cancer treating. Unlike most diagnostic methods used in oncology, the methods of nuclear medicine allow assessing not only the anatomic changes in the organ but also the disturbance of metabolic processes in tumors and surrounding tissues.

Benign neoplasms consist of well-differentiated cells, the structure and function of which is similar to normal tissues. The rate of their growth is relatively small, they do not germinate nearby tissues and do not give metastases. Life-threatening situations can occur only in those cases when the tumor compresses vital organs, main vessels, tracts and ducts or produces an excessive amount of hormones and other biologically active substances. Surgical removal of benign tumors usually provides a persistent recovery of the patient. Malignant tumors consist of undifferentiated cells that have an atypical structure and function. Cancer cells can be scattered in the body (for example, in leukemia) or limited to the cellular association of tumor tissue. Malignant neoplasms are characterized by rapid growth, and in the absence of adequate treatment they metastasize to remote areas of the body, which in turn become new centers of atypical tissue growth. In malignant cells disrupted synthesis of specialized proteins, and begins to produce biologically active substances, some of which stimulate neoangiogenesis, promote metastasis. Dissemination tumor occurs both in the lymphatic system and hematogenous route. Each localization of cancer is characterized by the typical location of metastases. For example, in colon cancer metastasis begins most often in liver, in breast cancer—in bone.

Radiopharmaceuticals used for the diagnosis and treatment of tumors can be divided into the following groups:
Radiopharmaceuticals that can accumulate in tissues surrounding the tumor
– in intact tissues;
– in tissues altered by the tumor.
Radiopharmaceuticals that can accumulate on the membranes of tumor cells
– for the "antigen-antibody" reaction;
– on the mechanism of cellular reception.
Radiopharmaceuticals that can accumulate in tumor cells
– specific;
– nonspecific.
Radiopharmaceuticals for sentinel lymph nodes detection

RADIOPHARMACEUTICALS THAT CAN ACCUMULATE IN INTACT TISSUES SURROUNDING THE TUMOR

This group of radiopharmaceuticals selectively accumulates in one or another tissue of the body and makes it possible to detect the presence of a tumor as a region of reduced accumulation of the agent. For example, a 99mTc colloid accumulating in Kupffer cells of the liver normally gives a uniform image, whereas a primary liver tumor or areas of its metastatic lesion are characterized by the appearance of "accumulation defects" of the radioactive agent corresponding to the localization of the neoplasm. It is quite obvious that this technique does not have high specificity, since any volumetric liver damage, for example, a cyst, is visualized in a similar way.

Other typical radiopharmaceuticals of this group include 99mTc pertechnetate [1] and iodine isotopes (123I or 131I), which have been used for many years to diagnose thyroid tumors. These radiopharmaceuticals, accumulating in thyroid tissue, allow diagnosing malignant neoplasms in it by the presence of defects in the accumulation of agents. A disadvantage of the technique is its low specificity, as gland cysts similarly visualized as areas of reduced accumulation of the radiopharmaceutical.

In recent years, studies with radiopharmaceuticals of this group lost their popularity, yielding to less costly ultrasonic methods.

RADIOPHARMACEUTICALS THAT CAN ACCUMULATE IN TISSUES ALTERED BY THE TUMOR

The use of radiopharmaceuticals of this group is based on the phenomenon of their increased accumulation in the tissue surrounding the tumor. For example, the tissue surrounding the bone tumor responds to its growth with increased osteoblastic activity. Phosphate complexes of 99mTc, accumulating in osteoblasts, allow visualization of bone metastases and primary bone tumors at the earliest stage of their development as "hot foci". Unfortunately, this highly sensitive method does not have high specificity, since enhanced accumulation of these radiopharmaceuticals in bone tissue can also be observed in fractures, osteomyelitis and some other diseases. The diagnostic accuracy of radionuclide techniques is enhanced when performed in the SPECT mode, especially when metastases are detected in the spine. In addition, the specificity of detection of malignant bone formation increases with the combination of SPECT and CT techniques.

Accumulation of phosphate complexes in osteoblasts is used in nuclear medicine for palliative therapy of bone metastases. Sm-153-oxabifore and Re-186-phosphate complexes are used for these purposes. These radionuclides affect the areas of osteoblastic activity with the help of β-radiation, and their γ-quanta (103 and 137 KeV, respectively) can be detected with a gamma camera, visualizing the distribution of radiopharmaceuticals in the body.

Strontium-89 is also very popular for the treatment of bone metastases. Being a biological analogue of calcium, this radionuclide accumulates both in normal bone tissue and in areas with increased osteoblastic activity. But the clearance of the radiopharmaceutical from the metastatic lesions is much slower than from intact tissue. Unlike 186Re and 153Sm, Strontium-89 is a pure β-emitter and with the help of a gamma camera it is impossible to register the distribution of this radiopharmaceutical in the body [1].

The second mechanism providing the phenomenon of hyperfixation of radiopharmaceuticals of this group in tissue sites surrounding the neoplasm is active angiogenesis induced in perifocal areas by biologically active malignant tumor factors. In this situation, the tumor is detected on the basis of increased accumulation of 99mTc erythrocytes in the intensively blood-supplying tissue regions surrounding the malignant tumor.

Unfortunately, the sensitivity and specificity of these techniques for tumor diagnosing is low. At the same time, some radionuclide therapy techniques are based on the phenomenon of enhanced blood supply to tumors, which are successfully used in the treatment of liver metastases. For these purposes, the introduction of 131I-lipidol, as well as Y-90-labeled resins or glass microspheres into the hepatic artery is used.

RADIOPHARMACEUTICALS THAT CAN ACCUMULATE ON THE MEMBRANES OF TUMOR CELLS FOR THE "ANTIGEN-ANTIBODY" REACTION

The diagnostic application of radiopharmaceuticals of this group in oncology is based on the reaction of labeled monoclonal antibodies with antigens of cancer cell membranes. In the diagnosis, both whole IgG-type antibodies and their fragments (Fab-fragments of antibody) were used [3]. Advantage Fab is a higher oncospecificity. However,

faster Fab's clearance from the blood, compared to large molecules of immunoglobulins, due to renal excretion can reduce the tumor/background ratio in a tumor with low blood flow.

One of the problems that arises during the synthesis of labeled antibodies is a decrease in immunospecificity during the formation of radiopharmaceuticals. One way to solve this problem is to obtain the "antibody-radionuclide" complex *in vivo*. In this case, first, intravenously injected antibodies, coupled with a chelate. After the accumulation the complex in the tumor patient is administered a radionuclide, which is connected to the chelate allows visualizing the tumor. The main advantage of this method is the reduction of non-specific binding of antibodies in combination with obtaining a high ratio of radioactivity "tumor/background" [4].

RADIOPHARMACEUTICALS THAT CAN ACCUMULATE ON THE MEMBRANES OF TUMOR CELLS ON THE MECHANISM OF CELLULAR RECEPTION

The use of such radiopharmaceuticals for diagnosis is based on the property of their affinity for certain receptors of tumor cell membranes.

Currently, the most frequently used radiopharmaceuticals of this type are somatostatin analogues—octreotide, labeled with 111In and 99mTc.

Somatostatin is a tetradecapeptide secreted by the hypothalamus, which suppresses the release of neuro-endocrine hormones (growth hormone, glucagon, insulin and gastrin). Somatostatin receptors, among which five subtypes are distinguished, are widely represented in normal tissues, but in many malignant tumors and in certain inflammatory diseases, the density of these receptors is significantly increased. This overexpression is observed in most neuroendocrine tumors, in lung cancer, and also in the peritumoral veins of some human tumors, which creates a basis for differentiating these tumors from other tissues by radionuclide diagnostics using radiopharmaceuticals selectively binding to somatostatin receptors.

These radiopharmaceuticals have been used to diagnose a number of neuroendocrine tumors (carcinoid, pheochromacytoma, paraganglioma, melanoma), lung cancer, neoplasms of the central nervous system and lymphomas. The sensitivity and specificity of such malignant tumors detection using 111In-osteotide exceeds 80% [5]. However, the diagnosis of liver cancer and spleen lesions with this radiopharmaceutical has low efficiency due to high level of non-specific accumulation of this indicator in the organs. 99mTc-octreotide is used primarily for the detection of lung cancer. The sensitivity of SPECT/CT of malignant solitary pulmonary tumors reaches 97% with a specificity of 73%.

In recent years, 123I and 99mTc labeled peptides have been found in oncological practice, which are also capable of binding to the membranes of tumor cells. Labeled vasoactive intestinal peptides are used to visualize malignant neoplasms of the gastrointestinal tract and pancreas; labeled α-melanocyte-stimulating hormone is used to diagnose melanoma; labeled insulin is used to diagnose hepatoma and labeled neuropeptides are used to detect small cell lung cancer.

RADIOPHARMACEUTICALS THAT CAN ACCUMULATE IN TUMOR CELLS BY SPECIFIC MECHANISM

Radiopharmaceuticals of this group are included in the specific metabolism of tumors (iodine isotopes 123I and 131I, 123I-methoyiod-benzyl guanidine (123I-MIBG), 131I-methoyiod-benzyl guanidine (131I-MIBG) pentavalent 99mTc (V)–DMSA).

Iodine-131 has been successfully used for more than 60 years to diagnose follicular and papillary thyroid cancer and, especially, its metastases [6].

Differentiated thyroid tumors retain the ability to capture iodine and include it in the synthesis of thyroid hormones. Malignant tumor in such cases is visualized as a "hot" focus, resembling a nodular thyrotoxic goiter, and metastases are detected as areas of extrathyroid ectopic accumulation.

It should be borne in mind that there is the possibility to obtain false-positive results due to the nonspecific uptake of iodine in the tissue of the salivary glands, as well as its excretion into the intestine and bladder. Low-differentiated forms of thyroid cancer appear on scintigrams as "accumulation defects", since atypical cells of these tumors lose their ability to metabolize iodine.

In recent years 123I has been used instead of 131I to perform radiodiagnostic procedures, which has a number of advantages: the optimal energy spectrum (159 KeV) for registration and a short half-life that helps to reduce the radiation dose to the patient.

In 1982, a group of scientists led by Professor Ann Arbor from the University of Michigan (USA) synthesized 123I-MIBG, which through the norepinephrine absorption mechanism is converted into catecholamines adrenergic nerve endings and adrenal medulla cells, thereby allowing visualization of the adrenal glands. In subsequent years, the high efficiency of the use of this radiopharmaceutical for the diagnosis of neuroendocrine tumors was shown, especially—pheochromocytoma, neuroblastoma, carcinoid, medullary thyroid cancer and paragangliomas. It should be noted that 131I-MIBG was effective for radionuclide therapy of these diseases.

Another radiopharmaceutical, specifically accumulated in the cells of medullary thyroid cancer, is pentavalent 99mTc (V)-DMSA. Scintigraphy with this agent is a highly specific technique for detecting this neoplasm, but the mechanism of accumulation of 99mTc (V)-DMSA in the tumor remains unexplored.

RADIOPHARMACEUTICALS THAT CAN ACCUMULATE IN TUMOR CELLS BY NONSPECIFIC MECHANISM

Gallium-67 citrate has been successfully used for many years as a radiopharmaceutical for the diagnosis of tumors. Recently, the mechanism of its accumulation in a tumor cell has been studied, determined by the fact that 67Ga after intravenous injection forms a complex with blood transferrin, which, in turn, binds to the receptors of some tumor cells. 67Ga-transferrin enters the cell through invagination of the cell membrane and, forming a complex with lactoferrin, remains in it.

67Ga-citrate has well established itself as a radiopharmaceutical for radionuclide diagnostics of lymphomas and small cell lung cancer. The literature describes application examples of the radiopharmaceutical for the detection of other malignancies. At the same time, nonspecific accumulation of 67Ga-citrate in the liver and excretion into the gastrointestinal tract limit its use for the diagnosis of abdominal tumors. In addition, 67Ga-citrate accumulates in the areas of infection and inflammation, which reduces the specificity of the method. Scintigraphy with this radiopharmaceutical has been successfully used to dynamically monitor a verified malignant neoplasm in the dynamics of chemo- or radiotherapy.

The isotopes of thallium (201Tl and 199Tl), being a biological analogue of potassium, are captured by the cell with the help of a sodium-potassium ATP-dependent pump and are localized in the mitochondria [8, 9]. These radiopharmaceuticals accumulate mainly in tissues with intensive energy metabolism (including atypical cells) and are widely used for the diagnosis of tumors, including neoplasms of bronchial tubes, lymphomas, thyroid cancer, bones and brain. Like 67Ga citrate, thallium isotopes are successfully used for the dynamic evaluation of chemo- or radiotherapy [9].

The non-specific positron-radiopharmaceutical—18F-fluorodeoxyglucose (18F-FDG) allows detecting a wide variety of malignant neoplasms with high sensitivity. The accumulation of this indicator in the cell is directly proportional to the efficiency of the e protein glucose transporter functioning and correlates with the activity of hexokinase II, the enzyme that realizes the exchange of the hydroxyl group of glucose for the phosphate complex of ATP. The phosphorylated metabolite of 18F-FDG loses its ability to transport through the cell membrane and remains intracellular. Thus, the high ratio of the concentration of radiopharmaceuticals "tumor/background" is achieved due to the significantly higher activity of hexokinase II in malignant cells. In recent years, there have been reports of the possible use of glucose labeled with technetium-99m as potential radiopharmaceutical for cancer diagnosis [10, 11].

The use of another nonspecific radiopharmaceutical for PET 11C-methionine for the diagnosis of tumors is based on a high level of amino acid metabolism in actively proliferating cells of malignant tumors. This indicator is used in the detection of lymphomas, malignant tumors of the neck and head.

Technetium-99m complexes with methoxy-isobutyl-isonitrile and tetrofosmin are actively used in nuclear oncology, thanks to the ability of these radiopharmaceuticals to accumulate in the mitochondria of malignant cells. Most of these indicators are used to detect breast cancer, larynx, lung tumors, lymphomas and myeloma [12–14].

RADIOPHARMACEUTICALS FOR SENTINEL LYMPH NODES DETECTION

Lymphoscintigraphy plays an important role in the diagnosis of lymphatic system in patients with edema of lower extremities. The method allows evaluating the function of lymphatic capillaries, transport of isotope through collectors and its accumulation in regional lymph nodes. Besides, radionuclide techniques have proven themselves to identify the so-called "sentinel" lymph nodes (SLN)—first lymph nodes on the path of lymph drainage from a malignant tumor. These nodes, filtering afferent lymph, become a "trap" for cancer cells, and that is why SLN

biopsy (followed by histological examination) is an objective diagnostic criterion for the spread of malignant process. It is believed that if the SLN are not affected by metastatic disease, all other regional lymph nodes remain intact [15]. The world practice has considerable experience in relation to radionuclide visualization of "sentinel" lymph nodes at melanoma and breast cancer. At tumors in other locations (lungs, head, neck, cervix, gastrointestinal tract) the effectiveness of this method is studied in scientific research [16, 17]. Optimal radiopharmaceutical to identify SLN is colloid labeled with technetium-99m. Determining factor in selecting indicator is the size is radioactive particles. Thus, according to Schauer A.J. et al. [14], a colloid with the size of the particle less than 50 nm can accumulate not only in SLN, but also in subsequent nodes. Particles bigger than 100 nm slowly migrate from injection site. Colloid with the size of the particle from 50 to 80 nm was considered optimal for detecting SLN. Currently, in the Russian Federation there are no registered radiopharmaceuticals for SLN imaging. In this regard, the Tomsk Cancer Research Institute and Tomsk Polytechnic University developed by the original radiopharmaceutical based on labeled with technetium-99m aluminum oxide (99mTc-Al2O3). An experimental and clinical study of this radiopharmaceutical showed that the accumulation level of 99mTc-Al2O3 in sentinel lymph nodes is several times higher in comparison with import agents, and its practical application will facilitate intraoperative identification of SLN [18].

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